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A COMPREHENSIVE PREBIOLOGICAL SCREEN FOR ECOTOXICOLOGIC EFFECTS

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Abstract — Simple properties of chemicals—the octanol–water partition coefficient (K_{ow}), Henry's Law constant (H_c) and biodegradability half-life ($t_{1/2}$) — provide a means of evaluating ecotoxicologic testing requirements prior to direct screening using various organisms. Based on potential for exposure, arrays of properties portending ecotoxicologic concern are suggested for bioaccumulation and chronic effects, multispecies–multimedia involvement, inhalation toxicology and abiotic atmospheric effects.

Keywords — Ecotoxicology Partition coefficient Henry's Law constant Biodegradation Bioaccumulation Chronicity Multimedia Atmospheric effects

INTRODUCTION

There is a need for a systematic screening system to be used prior to explicit testing of a chemical for ecotoxicologic effects and exposure potential. This need is particularly relevant to review of premanufacturing notices under the Toxic Substances Control Act [1], for which data must be developed regarding use (manufacture, marketing, applications) and risk (health and environmental impacts). The manufacturer must decide what data to gather, while the U.S. Environmental Protection Agency (EPA) must quickly determine whether testing is needed and, if so, explicitly of what nature and extent. A screen should not only suggest where testing is likely to reveal concerns regarding hazard or exposure but should also demarcate areas of low concern where testing may be counterproductive.

Measured physicochemical data, or those projected from quantitative structure–activity relationships (QSAR), can help in accurately directing testing of a candidate chemical for potential exposure and hazard [2,3]. Such information is available early in a chemical's "history." Experience and detailed analysis by expert groups [3–5] have shown that use of these data predicts much about the likelihood of a given chemical to be problematic, particularly if it is likely to be persistent, pervasive and partitioned into biota. Attention to these properties would have averted many of our current and past difficulties with chemicals in the environment.

The screen set forth here is limited to neutral or weakly ionized organic chemicals which react neither covalently nor relatively rapidly with biologic or other environmental materials. Although pri-

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marily meant for ecotoxicologic exposure and hazard (i.e., environmental impact), it also has implications for health assessment.

BASIC LOGIC

We are mostly concerned about properties of a chemical which permit it to affect ecosystems adversely over large extents of space and time. Accidents may happen and isolated misuse may occur, resulting in adverse consequences from acute episodes. A screen, integrated with a testing logic and an assessment strategy, should prepare society for dealing with these adverse consequences by identifying aspects requiring study. It should assure society that *no* chemical capable of irremediable harm is produced, distributed, used and disposed of without an adequate basis for management. Such information usually comes from testing, which must not be unnecessarily burdensome or stifle innovation [1].

For a new chemical (or one already in production but poorly understood), we cannot explicitly define exposure. However, on the basis of experience we can generalize sufficiently to know which kinds of exposures are possible. Therefore, we know where to look for possible problems of persistence and pervasiveness that may lead to lasting, continuous or iterative exposures, those likely to harm ecosystems.

The potential exposure to a hazardous chemical will be a function of the concentration of the chemical in the media wherein organisms are found and interact. The predicted environmental concentration (PEC) is affected by several factors, but appears to be most sensitive to those properties of the chemical which control the extent of partitioning between media and the lifetime of a molecule in any given medium [2,6].

The dominant partitioning relationships involved are between water and either biota (especially lipids) or soil–sediment on one hand, and between water and air on the other. The former can be indexed appropriately by the octanol–water partition coefficient (K_{ow}), while the latter is well represented by Henry's Law constant (H_c). These steady-state or equilibrium measures, however, must be considered for dynamic systems in which chemical and biological transformations may destroy or generate compounds of toxicological interest. Hence, the basic third property is the biotransformation rate (or suitable substitute) expressed as the half-life ($t_{1/2}$) of the chemical. The relationships between these three properties and their consequences in the environment form the basis for the screen.

The proposed screen assumes that combinations of properties confer environmental consequences, thus excluding certain possibilities and narrowing the focus to major scenarios. Examining the three-dimensional relationships initiates a process which highlights problems and limits concern regarding "nonproblems." Chemicals with similar potentials are grouped between sets of planes in space dimensionalized by log K_{ow}, log $t_{1/2}$ and log H_c. The rationales for designating these planes follow.

PARTITIONING AND PERSISTENCE

Log K_{ow} vs. log $t_{1/2}$

With few exceptions (noted later), chemicals that are not very soluble in water, if sufficiently stable, are partitioned into biota (especially lipids) and into soil–sediment (especially those with high organic matter content). The chemicals so sorbed may also be protected from biologic and physicochemical forces (e.g., those leading to transformation) which would otherwise reduce their effective concentration. We can index this property as log K_{ow}, which can be measured, calculated from chemical structure [7] or adequately estimated [8–10] from the measured solubility (S). Although complicated in sediment and terrestrial systems by the inherent structure of those environments, similar relationships have been found between log K_{ow} and both log K_{oc} (the soil sorption coefficient corrected for organic matter content) and dietary biocon-

centration factor (BCF_d) in birds and mammals [10,11].

Persistence of a chemical is much less easily characterized, since where a chemical is partitioned will determine which chemical and biological forces can effect its conversion to other more or less toxic entities. Some simple tests, however, provide sufficient information to infer the extent to which further determination of rates and pathways will be of value in exposure and hazard assessments. In addition to direct measurement of loss of parent compound and formation of metabolites, tests espoused by the Organization for Economic Cooperation and Development (OECD) [12] and guidance provided by the U.S. EPA [13] include measurement of rapid and complete mineralization through production of the theoretical amount of carbon dioxide (T_{CO_2}), consumption of dissolved oxygen (DO), or biological oxygen demand (BOD), and loss of dissolved organic carbon (DOC) in preconditioned aerobic sewage sludge. These general measures are given in descending order of applicability as substitutes for the preferred direct measurement of loss of parent compound and appearance of product(s).

The screening relationship of these two properties, log K_{ow} and biodegradability log $t_{½}$ (d), is illustrated in Figure 1. Boundaries of areas of "heavy concern," "concern" and "no concern" are established as follows:

(1) Chemicals with log $t_{½} < -1$ (0.1 d) (Zone 0) are very unlikely to cause ecotoxicologic problems unless local release rate exceeds biodegradation rate for some time. Moreover, testing them for chronic effects may be pointless, as they are likely to be difficult to handle in standard tests.

(2) Chemicals with log $t_{½} < 0.6$ (4 d) (Zones 0 and B) will be > 90% degraded within a fraction of the lifetime of most vertebrates and invertebrates or of a plant's growing season. Such chemicals would be of little concern for ecotoxicologic effects if there were no complications arising from other properties.

(3) Chemicals with log $t_{½} > 1.146$ (14 d) may exist (> 10% initial concentration) for a substantial fraction of an animal's life or a plant's growing season. This is sufficient condition to consider it of heavy concern regarding chronic action (Zones A, C and E).

(4) Chemicals with log $K_{ow} < 2.5$ (Zones 0, D and E) do not bioaccumulate in terrestrial animals at a concentration of about one-third that of the diet or in fish at a ratio of 300 times that in the medium. Bioaccumulation is not of serious concern (Zones B and C) unless log K_{ow} exceeds 3.5 (Zone A), whereas 94% of the tested chemicals with log $K_{ow} >$ 4.5 have log $BCF_d > -0.5$ [10].

(5) All chemicals with log $K_{ow} > 3.5$ (Zone A) are of heavy concern for bioaccumulation (and hence chronic action on consumers), unless mitigated by low persistence (Zone B). Typical examples are the nonaccumulating synthetic and natural pyrethroids, which have log $K_{ow} > 5$ and $t_{½}$ of minutes or hours.

(6) There may be additional boundaries of interest in testing. Chemicals with log $K_{ow} > 7$ or log $S < -10$ (g/L) *tend* to be so insoluble as to present special experimental difficulties. Bioaccumulation may be significantly diminished for chemicals with log $K_{ow} > 7$ or mol wt > 550–650, due to steric problems (molecular cross section) in passing through membranes and slow rates of solution. Thus, chemicals with properties beyond this boundary (Zone F) are not likely to be ecotoxicologically significant and tests may be both difficult and uninformative.

(7) Chemicals with combinations of properties between these limits may be of heavy concern (Zone A) if:

$$\log K_{ow} + 1.631 \log t_{½} \geq 5.37 \quad (1)$$

(between the limits of $-1 < \log t_{½} < 1.146$ and of $7 > \log K_{ow} > 3.5$).

(8) Those chemicals not of heavy concern would still be of concern (Zone B) if:

$$\log K_{ow} + 0.625 \log t_{½} \leq 2.875 \quad (2)$$

(between the limits of $-1 < \log t_{½} < 0.6$ and $3.5 > \log K_{ow} > 2.5$).

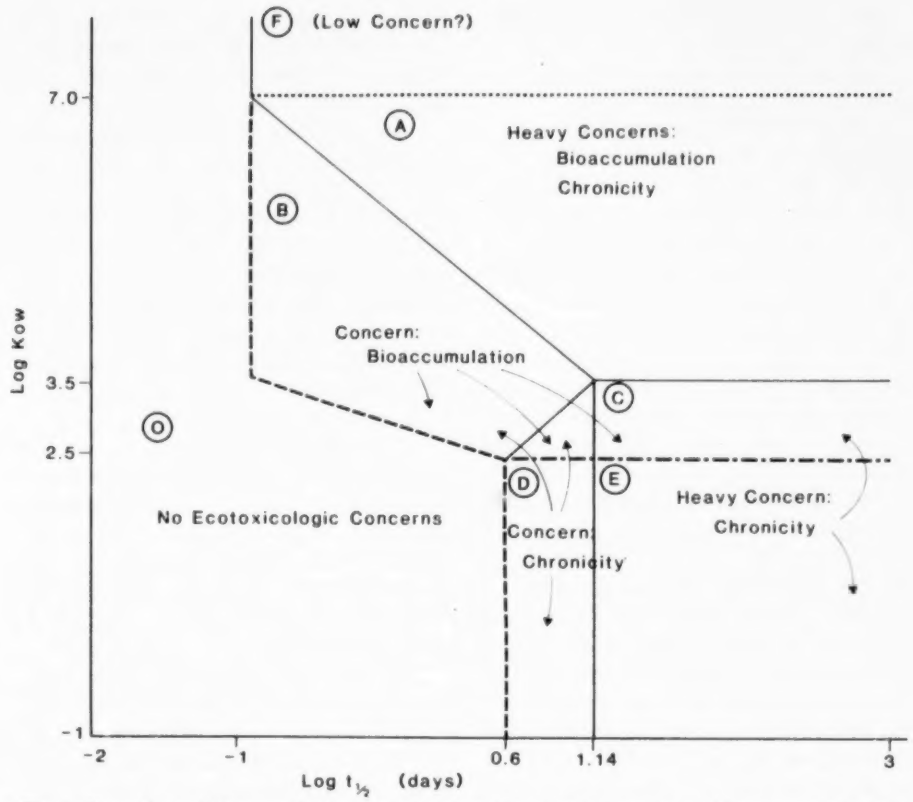

Fig. 1. Chronicity and bioaccumulation potential: comparison of log K_{ow} and log $t_{½}$. Heavy concern for both chronicity and bioaccumulation (Zone A) is above the line of Eq. 1 and log $K_{ow} \geq 3.5$ (see text). Zones C and E have heavy concern for chronicity, but Zone E is of no concern regarding bioaccumulation. Zones B and D are of concern regarding chronicity, but only Zone B is of concern regarding bioaccumulation. These zones are separated by the arbitrary line connecting log $t_{½} = 0.6$, log $K_{ow} = 2.5$ with log $t_{½} = 1.146$, log $K_{ow} = 3.5$. Zone 0 is below and to the left of Eq. 2 and other criteria for no concern. Zone F is above log $K_{ow} < 7$.

The above divisions are based on data in which we have some confidence *in toto*, but for which there may be uncertainty regarding a particular measurement for any given chemical. Some measure of biological activity and factors of production, use and disposal should be taken into account before waiving further testing of a chemical evaluated as being of no concern for ecotoxicological effects.

Log H_c vs. log $t_{½}$

Henry's Law constant (H_c) is important in estimating the rate of loss of a chemical from water [14,15] or soil [15]. Smith et al. [15] found an excellent linear relationship between log H_c and volatilization half-life (HT_v) of chemicals in either static (lakes, ponds) or moving waters (streams, rivers), which may be approximated by:

$$\log HT_v = -0.42 \log H_c + 0.6 \quad (3)$$

where HT_t is the half-time for dissipation due to volatility and biodegradation (i.e., $1/HT_t = 1/HT_v + 1/t_{½}$).

Figure 2 shows the isokinetic lines (Eq. 4, below) for which the combination of volatilization and biodegradation is expected to produce aquatic half-lives of 0.1, 4 and 14 d.

$$\log H_c = 2.381 \log \left(\frac{1}{HT_t} - \frac{1}{t_{½}}\right) - 1.429 \quad (4)$$

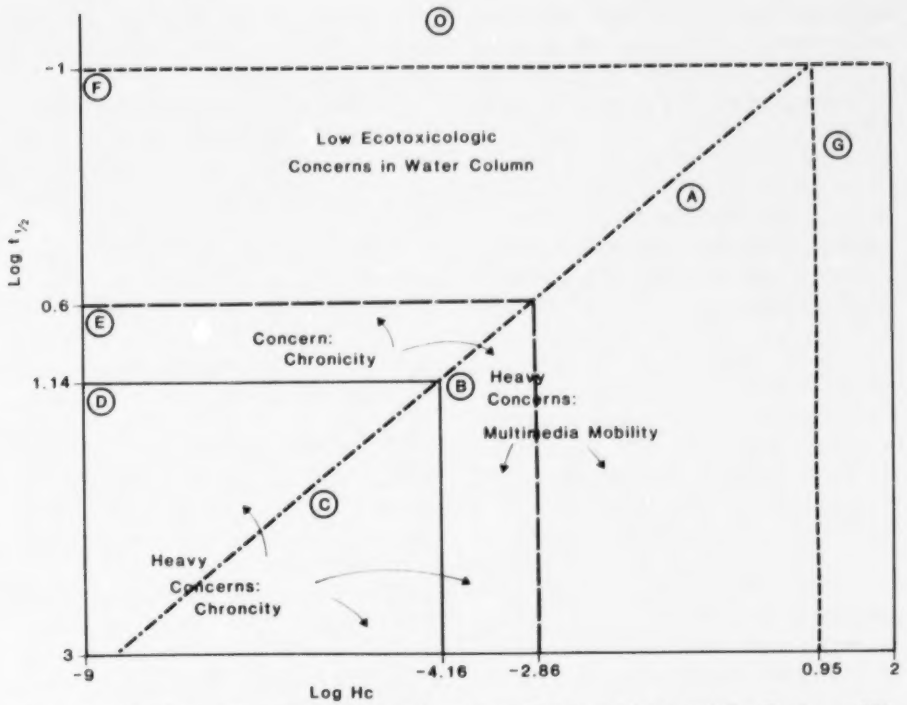

Fig. 2. Chronicity and mobility: comparison of log H_c and log $t_{½}$. The diagonal isodynamic line (Eq. 4, $t_{½} = HT_v = 2\ HT_l$) separates zones of no concern for multimedia mobility (D–F) from those of concern (A–C). Isokinetic lines (Eq. 4, $t_{½} = 14$, 4 and 0.1 d, respectively) separate areas of low mobility (Zones C and D) from those of higher mobility (Zones A and B) and hence heavy concern for multimedia–multispecies involvement. Zones C and D are of heavy concern for chronicity, Zones B and E are of concern, and Zone F is of no concern. Zone G is of concern regarding mobility from water. Zone A is of no concern regarding aquatic effects in the water column. Zone 0 is of no direct ecotoxicologic concern.

Due to the shape of the hyperbolic curves, the criteria are adequately expressed as the asymptoes ($t_{½} \rightarrow \infty$): log $H_c = -4.16$ and log $t_{½} = 1.146$ for heavy concern (Zones C and D) log $H_c = -2.86$ and log $t_{½} = 0.6$ for concern (Zones B and E) and log $H_c = 0.95$ and log $t_{½} = -1$ for low concern (Zones A and F). Chemicals with log $H_c > 2$ (Zone 0) will largely be gases and hence pose little direct ecotoxicological threat. Indirect problems (photochemical smog, stratospheric modification) and health implications (inhalation exposure) may, however, be very significant.

Because of problems in determining or estimating H_c accurately and the deviation from linearity of the relationship of log H_c to log HT_v at high volatilities [15], Zone F cannot be designated *per se* as being of no concern. However, chemicals within that zone may have aquatic half-times reduced sufficiently so as to no longer be a threat within the water column.

PERVASIVENESS

Log H_c vs. log $t_{½}$

As noted earlier, the pervasiveness of a chemical is as problematic as its persistence. We have no simple measure of pervasiveness, although it may be indicated by the concentration–frequency reports of chemicals in broad monitoring programs. Pervasiveness can occur through widespread manufacture, multiple product use

and/or multiple disposal routes. Pervasiveness is supported or augmented, however, by persistence and chemical mobility between media. Part of that mobility can be through high log K_{ow} values, such that chemicals of low volatility or solubility are advectively distributed as sorbed materials on dusts and sediments. More frequently, however, we see chemicals moving by volatilization out of water before treatment or off of soil after application. In the pelagic zone of waters with low suspended solids and organic matter, a high proportion of chemical volatilizing (as opposed to degrading) reflects an adverse potential for impact on other ecosystems. Thus, a chemical for which volatility exceeds biodegradability must be examined in more media (i.e., habitats) and hence with more species.

Figure 2 is divided by an isodynamic line ($t_{½} = HT_v = 2\ HT_t$) separating chemicals with greater mobility and stability (Zones A and B) from those with greater water solubility and biodegradability (Zones E and F). This line is of less importance in dividing Zones C and D, in which chemicals tend to remain in the medium in which they are deposited.

Log K_{ow} vs. log H_c

Comparative mobility due to volatilization also is affected by the proclivity of the chemical, as reflected by log K_{ow}, to be bound to organic matter, lipids, etc. The properties are not, however, fully independent variables. MacKay, et al. [14] showed that H_c could be empirically related to K_{ow} and boiling point–melting point. If the relative tendencies for a chemical to leave the aqueous phase (by sorption or volatilization) are about opposite and equal (Eq. 5): a useful set of criteria for mobilization may be established (Fig. 3):

$$\log H_c + \log K_{ow} = A \qquad (5)$$

(1) Chemicals for which $A \geqq +1$ and log $K_{ow} > 3.5$ may be strongly suspected of being very mobile from water to biota, soils and sediment, thus creating the widest possible exposure. Hence, they are of heavy concern for multimedia exposure and pervasiveness (Zone A).

(2) Heavy concerns about bioaccumulation (Zones A and B) extend to $A \geqq -1$ for log $K_{ow} > 3.5$, since reduced mobility in the vapor phase would promote dietary and contact exposure *in situ*.

(3) Because of very high mobility, chemicals with log $K_{ow} < 2.5$ and $A \geqq +1$ (Zone C) are of no *direct* ecotoxicologic concern, but rather raise questions of indirect effects (e.g., stratospheric modification) and inhalation toxicology in occupational exposures.

(4) For chemicals with $A \leqq -1$ and log $K_{ow} < 3.5$ (Zone 0), concern is for movement in the water column leading to leaching, plant uptake and drinking water toxicologic effects.

(5) For chemicals with log $K_{ow} > 7$ (Zone F) and log $K_{ow} > 4.5$ for $A \leqq -1$ (Zone E), the concerns are low because mobility is severely reduced. Similarly, chemicals with log $K_{ow} > 3.5$ and log $H_c > 2$ are of no practical concern (Zone 0) for ecotoxicologic effects.

(6) Each of these zones of heavy concern is surrounded by zones of concern which often overlap, especially in the central part. However, each heavy concern excludes all other heavy concerns (except for Zones A and B).

COMPREHENSIVE SCREEN

From the above discussion, one may exposit a comprehensive prebiological screen based on a relatively small amount of information: chemical structure, calculated (but preferably measured) values of log K_{ow} and log H_c and a measure of biodegradability. Combining Figures 1, 2 and 3 establishes three-dimensional spaces of varying degrees of concern for persistence, bioaccumulation and multimedia–multispecies exposure. Figure 4 illustrates the translation of the criteria and Figures 1 through 3 to planes in three-dimensional space.

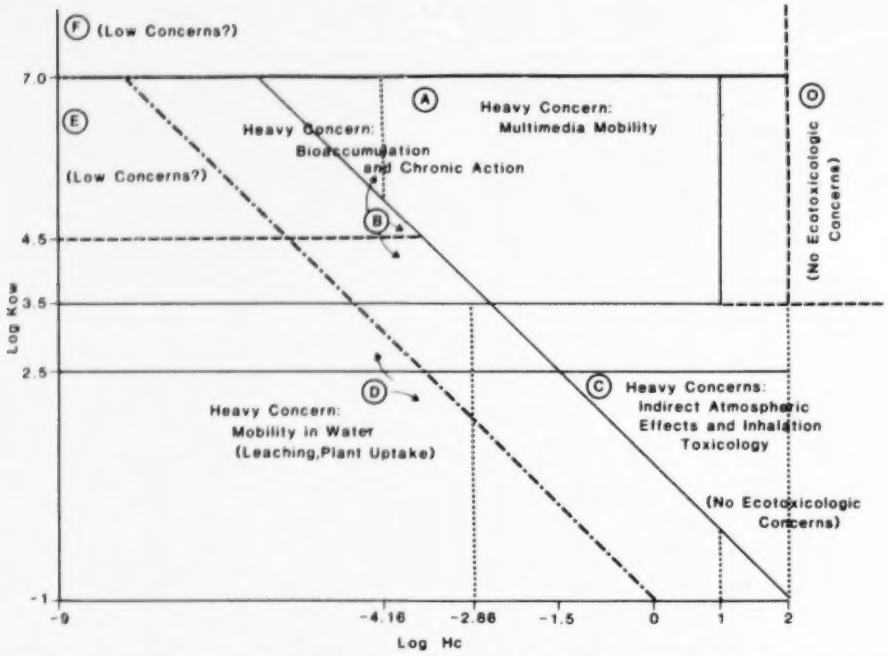

Fig. 3. Mobility and multimedia exposure: comparison of log K_{ow} and log $t_{1/2}$. The area is divided into zones by the diagonal lines of Eq. 5 (A = −1 and +1), the horizontal lines of log K_{ow} = 2.5 and 3.5 (from Fig. 1) and the vertical lines at log H_c = −4.16, −2.86 and +1 (from Fig. 2) and log H_c = 2 (by assumption, see text). Zone A has heavy multimedia–multispecies concerns; Zones A and B have heavy concerns regarding bioaccumulation. Zone C is of heavy concern regarding indirect atmospheric problems, including ozone depletion, oxidant generation and inhalation toxicology. The remainder are of no concern regarding atmospheric effects *per se*. Zone D is of heavy concern for direct effects in the water column, including leaching to and flow through groundwater and plant root uptake. Zones E and F are of low ecotoxicologic concern due to very low mobility.

Screening is accomplished (Fig. 5) by locating coordinates for log K_{ow}, log $t_{1/2}$ and log H_c in three-dimensional space.[1] If biodegradation of a chemical is indeterminant, a default value of 2 is used. This has the effect of focusing attention on measured biodegradation. Exclusions noted earlier (highly ionized, organometallic, covalently reacting and/or gaseous chemicals — those which qualify as polymers) must be taken into account.

Based on location, tests appropriate to the concerns attendant thereto can be recommended. As illustrated in Figure 6, these range from tests in a minimum data set (rat or mouse acute oral LD_{50}, rainbow trout 96-h LC_{50}, *Daphnia* 24 h EC_{50} and 14-d reproduction test, algal assay, or seed germination–early seedling growth) to a so-called "Mount" or multispecies cluster [5] of five to eight aquatic and terrestrial vertebrates and invertebrates evaluated for toxicity on a mg/kg basis, and onto extended multigenerational chronic studies and bioaccumulation testing. Parallel fate testing might range from the minimum data set, e.g., as required by OECD [12], through multimedia and multispecies transformations under aerobic and anaerobic conditions. Similarly, modeling requirements would proceed from PEC calculations [3] to transport and exposure

[1] A computer program in Applesoft BASIC is available to identify the nature and extent of concerns set forth in this screen, along with suggested testing appropriate to these concerns. A draft copy can be obtained by submission of an initialized 5¼-inch diskette to the author. Alternatively, the draft computer program listing is available on request.

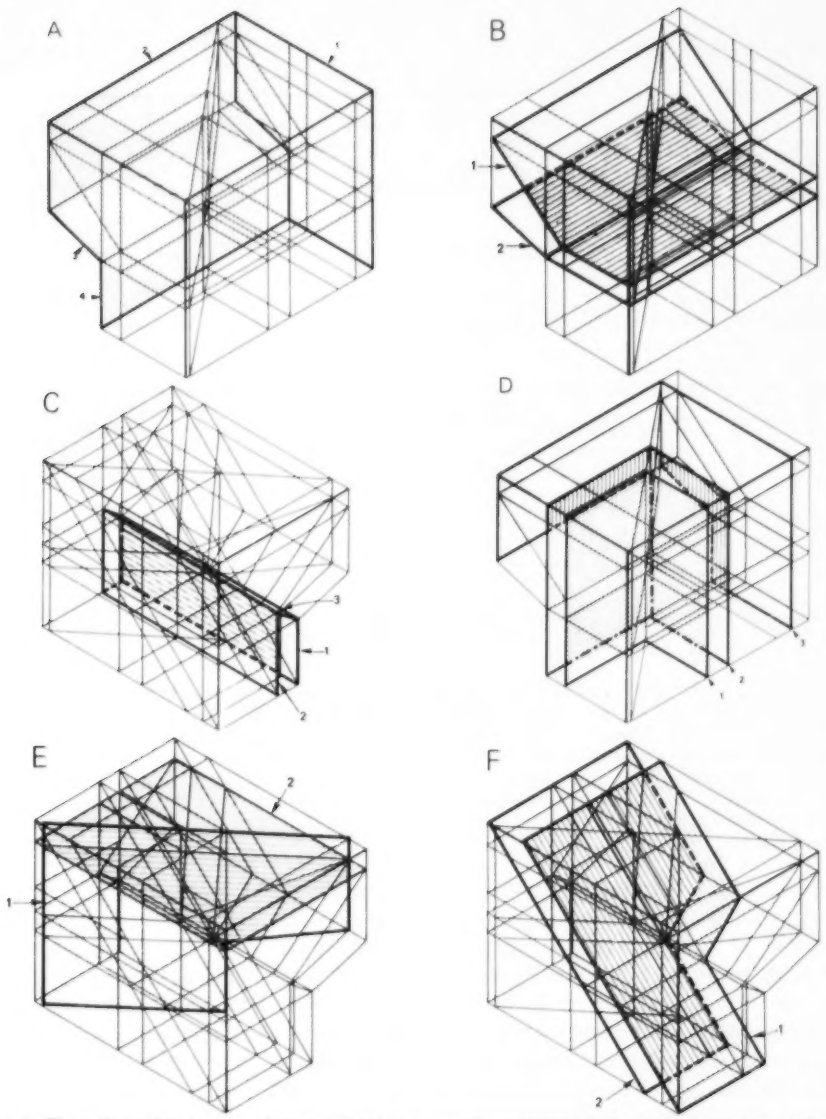

Fig. 4. Three-dimensional space of ecotoxicological concerns: orthographic views of planes from Figures 1 through 3.

A: Limits of no concern for direct ecotoxicologic effect are planes at (1) log $H_c = 2$, (2) log $t_{1/2} = -1$, (3) Eq. 2, and (4) log $t_{1/2} = 0.6$ for log $K_{ow} < 2.5$. These form the back and right side in the right oblique view.

B: Shown in a right oblique view are the planes of (1) heavy concern for bioaccumulation and chronicity (barred) at Eq. 1 and log $K_{ow} = 3.5$ (barred), and (2) concern at Eq. 2 and log $K_{ow} = 2.5$ (shaded).

C: The planes of (1) concern (barred) at log $t_{1/2} = 0.6$ and (2) heavy concern (shaded) at log $t_{1/2} = 1.146$ for chronicity but not bioaccumulation are connected by a plane (3) (stippled) between log $t_{1/2} = 0.6$, log $K_{ow} = 2.5$ and log $t_{1/2} = 1.146$, log $K_{ow} = 3.5$ (left oblique view).

D: The isokinetic planes of Figure 2 are shown as (1) $t_{1/2} = 14$ d (horizontal barred), (2) $t_{1/2} = 4$ d (vertical barred) and (3) $t_{1/2} = 0.1$ d (stippled) (right oblique view).

E: The isodynamic plane (1) from Figure 2 (Eq. 4, $t_{1/2} = HT_v = 2HT_t$) is shown connecting the corners of the isokinetic planes of Figure 4D; the upper limit plane for heavy bioaccumulation is shown (2).

F: The diagonal planes of Eq. 5 are shown as (1) $A = +1$ (barred) and (2) $A = -1$ (shaded).

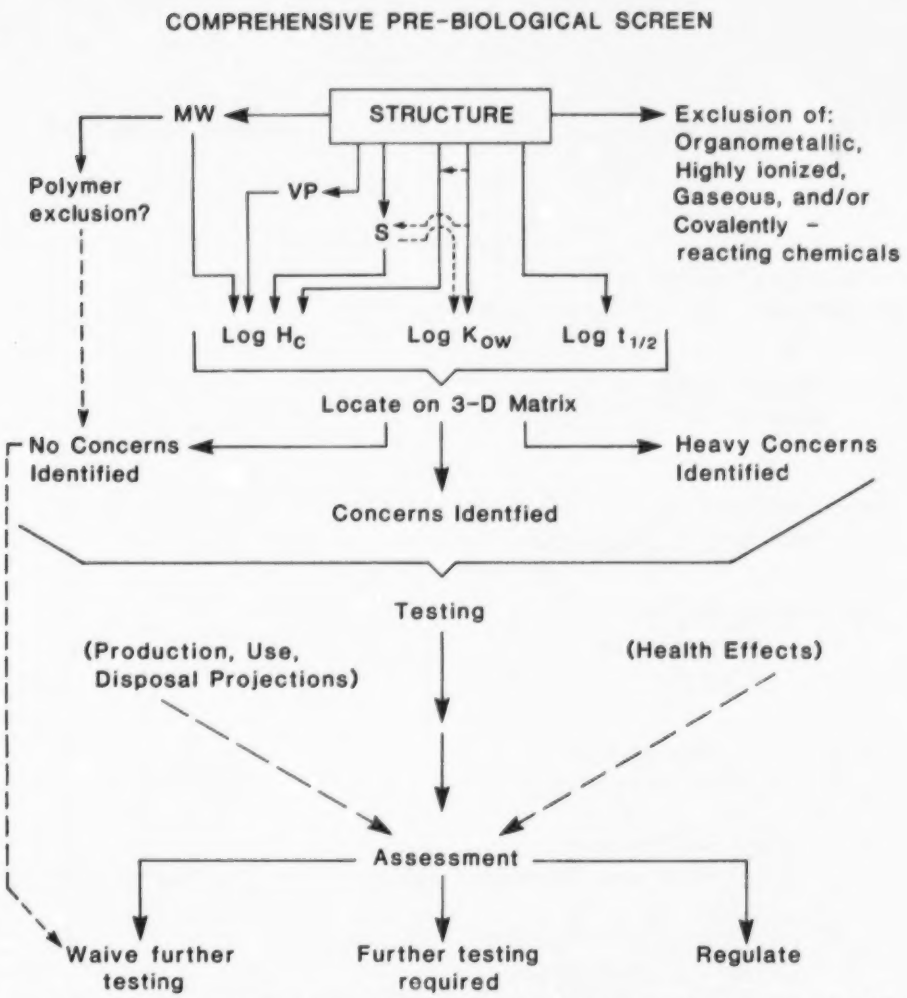

Fig. 5. Comprehensive prebiological screening system. Data derived from structure (MW, molecular weight; VP, vapor pressure; S, solubility) can be used to estimate Henry's Law Constant (H_c) and octanol–water partition coefficient (K_{ow}). Half-life ($t_{1/2}$) of biodegradation/biotransformation must be determined. These data are used in the screen to locate any areas of concern which, in turn, identify testing needs. Consequently, ecotoxicologic testing results are combined with health effects testing data and production, use and disposal projections for assessment of hazard.

scenarios, as in the exposure assessment model system (EXAMS) [6] or terrestrial exposure assessment model (TEA) [17] and through microcosms or field enclosures on to field testing.

The exact boundaries of testing keys and triggers in Figures 1 through 3 are still incomplete. The following expository examples show how the screen might be of use.

(1) Chemical A ($\log K_{ow} = 4.5$, $\log t_{½} = 2$ and $\log H_c = -2.5$) is located in a space with heavy concerns for multispecies–multimedia involvement (Fig. 7A) and bioaccumulation and chronicity (Fig. 7B). It can be anticipated that it will require the full extent of testing, with acute and subchronic tests acting as range-finding stages for chronic and multi-generational studies.

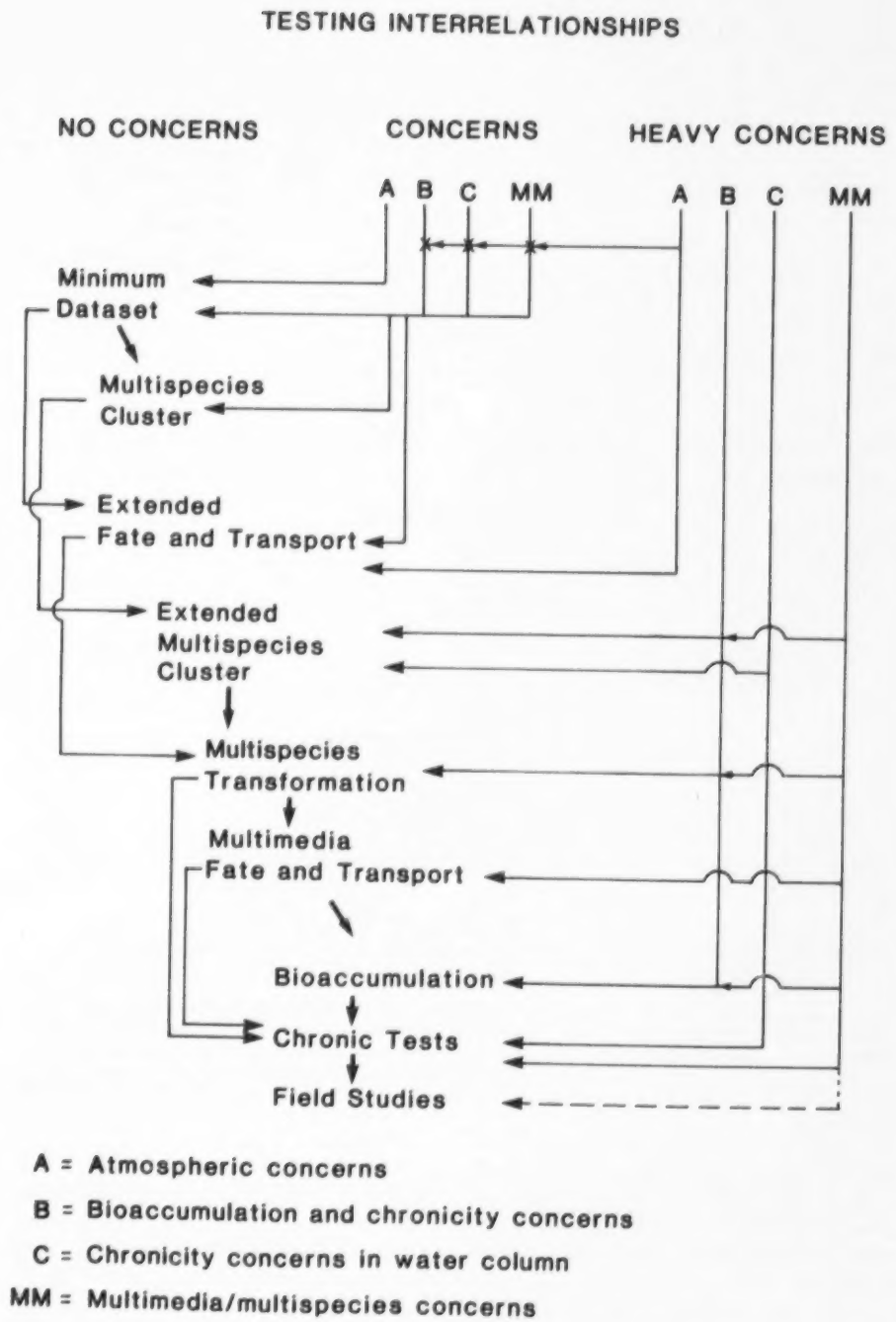

Fig. 6. Testing interrelationships from the prebiological screen. Waiver of further testing must consider minimal measures of biologic activity and health effects testing data in relation to production, use and disposal.

Complete multimedia fate testing is anticipated, and complete data development for modeling will be required for field studies. Approximately 94% of the tested chemicals in this space have been demonstrated to be bioaccumulators and were either banned or severely restricted as a consequence of adverse health and ecotoxicologic effects.

(2) Chemical B ($\log K_{ow} = 2.3, \log t_{1/2} = 2.5$ and $\log H_c = 1.5$) is in a space with heavy concern for atmospheric problems and inhalation toxicity (Fig. 7C), but of no direct ecotoxicologic concern. Hence, it should be keyed to the minimum bioactivity tests with an intention to waive further effects tests other than those for occupational health. Testing for hydrolysis and atmospheric photochemical and oxidative rates may be required for dispersion model testing and evaluation of abiotic impacts. Plant fumigation tests may be appropriate.

(3) Chemical C ($\log K_{ow} = 3.3, \log t_{1/2} = 1.1$ and $\log H_c = -3.5$ is located in a space bordering a number of ecotoxicologic concerns, and much of what might be anticipated for it will depend on the accuracy of the measurements yielding the coordinates. Hence, testing should focus on confirmation of properties (by development of a modeling data base), exploration of selective toxicity by testing at least at the "Mount cluster" level and then comparing the modeling scenarios with bioactivity test results. About 50% of the chemicals in this space are bioaccumulated and several function as systemic toxicants in plants. Thus, preliminary testing is needed to ascertain the direction and extent of chronic tests.

(4) Chemical D ($\log K_{ow} = 2.7, \log t_{1/2} = 0.4$ and $\log H_c = -6.9$) is of no direct ecotoxicologic concern, but it should be tested minimally for bioactivity before waiving further testing. If $t_{1/2}$ were determined in unacclimated media as the maximum value of parent compound loss in rapid and complete biodegradation, cause for waiver of further tests would be strengthened. Of course, waiver would not preclude testing later if significant new uses, greatly expanded production and distribution or adverse use experience occurred.

(5) Chemical E ($\log K_{ow} = 2.2, \log t_{1/2} = 1.3$ and $\log H_c = -5.4$) is of heavy concern for chronicity in aquatic species, for plant uptake (and possible herbicidal action) and for leaching (and hence drinking water toxicology) (Fig. 7D). Emphasis in testing should be on an aquatic cluster of vertebrates and invertebrates from the water column and on vascular plants. Chronic testing for reproductive effects in aquatic vertebrates is indicated, as may be similar testing for avian and mammalian species. Fate testing should include both aerobic and anaerobic processes in soil and sediments as part of data base development for modeling scenarios for comparison with bioactivity test results.

DISCUSSION

The prebiological screen will benefit from criticism and further definition of testing implications. One is struck by the complexity of the resulting three-dimensional array of the simplest set of characteristics of a chemical. Development of rules for an *n*-dimensional array will be afforded by QSAR regarding both those classes of chemicals now excluded and bioactivity results. How any multidimensional array might be exposited and comprehended effectively is a major question for future efforts.

Evaluation of the adequacy of this model is under way. Much will depend on the two-way acceptability (between regulators and the regulated industry) on the concepts embodied in it. Figures 1 and 3 are the most incisive for bioaccumulation potential, which has been measured for only 70% of the 129 priority pollutants [18]. Figure 2 incorporates features of mobility not shown in the others.

One clear lesson evident from the three-dimensional array is that properties of chemicals consistent with a specific use tend to result in similar outcomes. The desirable

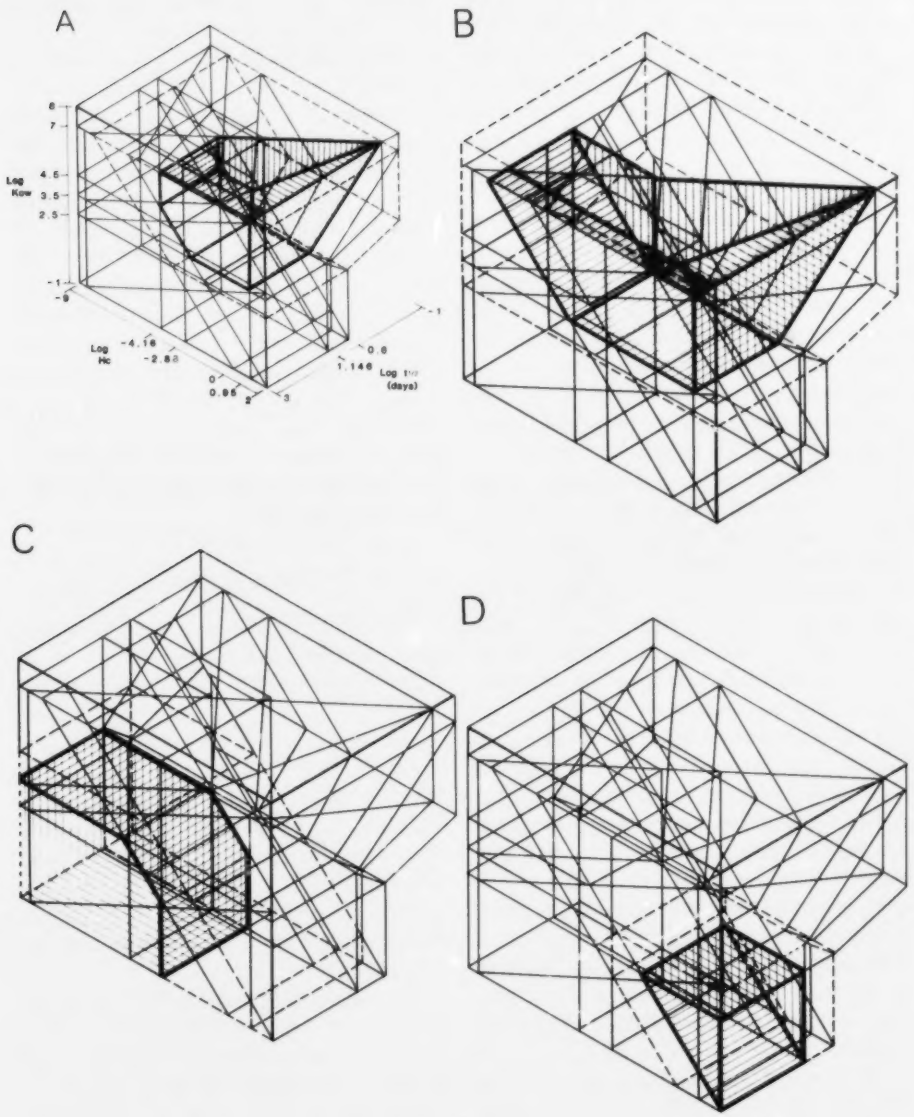

Fig. 7. Zone of ecotoxicologic concerns. Space of heavy concern is barred; space of concern is outlined in heavy broken line/dotted line. Planes are identified as in Figure 4.

A: Multimedia—multispecies involvement. Heavy concern is set off by B(1), D(2), D(3), E and F(1); concerns are limited by A(1), A(2), B(2) and F(2).

B Chronicity and bioaccumulation. Heavy concern is bounded by B(1), D(1), D(3), E and F(2); concern is bounded by A(1), A(2), and B(2).

C: Chronicity only. Heavy concern is bounded by B(1), C(2), D(2) and F(2); concern is bounded by A(4), D(2), D(3) and F(1).

D: Atmospheric problems. Heavy concerns are bounded by B(2), C(2) and F(1); concerns are limited by B(1), C(1), C(3), D(2) and F(2).

properties of a hydraulic fluid, persistent insecticide or transformer fluid are the consequence of physicochemical characteristics which result in similiar environmental distributions and biological activities for substitutes. Only by manipulating these properties (especially transformation) can an acceptable substitute be identified.

The testing ramifications for chemicals of heavy concern include increased direct testing costs, a longer time to decision and other demands expanding the cost of marketing a new chemical. Attention to this prebiological screen should alert manufacturers and regulators and enable them to prevent problems that have been encountered in the past. Hopefully, it will permit timely agreement as to the future course of testing of useful products.

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